AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Selective Serotonin Reuptake Inhibitors and Cataract Risk

A Case-Control Analysis

Claudia Becker, PhD,[1] Susan S. Jick, DSc,[2] Christoph R. Meier, PhD[1,2,3]

Purpose: Use of selective serotonin reuptake inhibitors (SSRIs) has been associated with an increased cataract risk. We aimed to assess cataract risk after exposure to SSRI or to other antidepressant drugs in a large electronic primary care database.

Design: Case-control study.

Participants: The study population was derived from the UK-based Clinical Practice Research Datalink (CPRD). We included patients with first-time cataract aged ≥40 years between 1995 and 2015 and an equal number of cataract-free controls matched on age, sex, general practice, date of cataract recording (i.e., index date), and years of history in the CPRD before the index date.

Methods: We conducted conditional logistic regression analyses adjusted for body mass index, smoking, hypertension, diabetes, and systemic steroid use. Exposure of interest was the number of SSRI prescriptions and prescriptions for other antidepressant drugs. We further explored mutually exclusive use of single SSRI substances. In sensitivity analyses, we shifted the index date backwards by 2 years, and we restricted our analyses to cases and controls without a prior glaucoma diagnosis.

Main Outcome Measures: Relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: We identified 206 931 cataract cases and the same number of matched controls. Current long-term use of SSRI (≥20 prescriptions) was not associated with an increased cataract risk (adjusted OR, 0.99; 95% CI, 0.94−1.03). However, in a subset of patients aged 40 to 64 years, we found a slightly increased risk of cataract for long-term SSRI users (adjusted OR, 1.24; 95% CI, 1.15−1.34) compared with nonusers.

Conclusions: In these data, use of SSRI was not associated with an increased risk of cataract. The slightly increased OR for individuals younger than 65 years of age in association with long-term SSRI use needs to be investigated in further studies. *Ophthalmology 2017;■:1−5 © 2017 by the American Academy of Ophthalmology*

Cataract is defined as a decrease in the transparency of the crystalline lens and is considered the primary cause of blindness worldwide.[1] Known risk factors are advanced age, smoking,[2] exposure to sunlight,[3] and use of corticosteroids.[4,5] Diabetes has been associated with an increased risk of cataract.[6,7]

Little is known about the association between use of antidepressant drugs and risk of developing cataract. Amitriptyline exposure has been associated with an increased risk of cortical cataract.[8] Animal studies have identified serotonin receptors in the lens[9] and provided evidence that serotonin can increase lens opacity.[10] Findings from 2 recent population-based studies from Canada and the United States found a tendency toward an increased risk of cataract in current users of SSRIs (relative risk, 1.15; 95% confidence interval [CI], 1.08−1.23)[11] and for SSRI use of 1 year or more (odds ratio [OR], 1.36; 95% CI, 1.23−1.51).[12] In analyses of single selective serotonin reuptake inhibitors (SSRI) substances, several SSRIs were shown to increase the risk of cataract[11,12] whereof citalopram yielded the highest OR of 1.53 (95% CI, 1.33−1.77).[12] The aim of this study was to quantify cataract risk associated with previous exposure to SSRIs within a large and well-validated primary-care database from the United Kingdom.

Methods

Data Source

We performed a retrospective case-control study using data from the Clinical Practice Research Datalink (CPRD). This database provides health care information on some 10 million patients in the United Kingdom and has been described in detail.[13,14] General practitioners (GPs) record information on demographics, diagnoses, and drug prescriptions, as well as on patient referrals and hospital admissions, using standardized coding systems. The GPs generate prescriptions directly from the computer, and this information is automatically transcribed into individual computerized patient records. In addition, the CPRD records contain information on body mass index (BMI) and lifestyle variables, including alcohol consumption and smoking. Recorded information on drug exposure and on diagnoses has been validated repeatedly and has proven to be of high quality.[15,16] The CPRD currently covers approximately 7% of the UK population, and enrolled patients are representative of the United Kingdom with regard to age, sex, and

http://dx.doi.org/10.1016/j.ophtha.2017.05.002
ISSN 0161-6420/17

BMI distribution.[17] The CPRD is managed by the Medicines and Healthcare Products Regulatory Agency in the United Kingdom. The study protocol (14_011R) was reviewed and approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research. The investigators had access to anonymous information only.

Study Design and Population

We conducted a matched case-control analysis. Cases were all persons in the base population aged 40 years or more between January 1995 and December 2015 who had a recorded incident diagnosis of cataract or cataract surgery. The date of the first cataract recording will subsequently be referred to as "index date." We excluded all patients with a recorded diagnosis of human immunodeficiency virus, alcoholism, or any malignancy (except nonmelanoma skin cancer), as well as those with less than 3 years of medical history in the CPRD computer record before the index date. We pair-matched at random 1 control patient without evidence of cataract to each case on calendar time (same index date), age, sex, general practice, and number of years of active history in the CPRD before the index date. We applied the same exclusion criteria to controls as to cases.

Exposure to Selective Serotonin Reuptake Inhibitors or other Antidepressant Agents

We identified prescriptions for SSRIs and other antidepressant drugs (tricyclic antidepressants [TCAs], serotonin noradrenalin reuptake inhibitors, monoamine oxidase inhibitors, or others) documented in the computer records before the index date. We classified patients by the extent of exposure to antidepressant drugs according to the recorded number of prescriptions received before the index date (3 categories for SSRI use: short-term 1−4, medium-term 5−19, or long-term use ≥20 prescriptions). We further evaluated the number of prescriptions according to the recency of the last prescription (current use: last prescription ≤30 days before the index date, recent use: 31−365 days, past use: >365 days). We compared use of each antidepressant drug class with nonuse of that drug class and adjusted the analyses for sequential or concurrent use of other antidepressant drugs in the multivariate model. We conducted further analyses stratified by sex and age (<65 vs. ≥65 years of age). Furthermore, we ran a model in which we classified SSRI users into mutually exclusive groups to explore the association between individual SSRIs and the risk of cataract; thus, we focused on mono-users of each SSRI and categorized patients who switched between SSRIs separately.

Statistical Analysis

We conducted conditional logistic regression analyses using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC) to calculate relative risk estimates as ORs with 95% CI. We controlled for the mentioned matching variables and for smoking status (never, ex-smoker, current, or unknown), BMI (<25, 25−29.9, ≥30 kg/m^2 or unknown), exposure to systemic (i.e., oral and parenteral) glucocorticoids, as well as hypertension and diabetes mellitus in the multivariate model. We included these confounders on the basis of previous clinical knowledge. We conducted several sensitivity analyses: First, we shifted the index date backwards in time by 2 years to account for the latency of the cataract recording and to ensure that potential exposure to antidepressant drugs occurred before cataract development. Second, we restricted our analysis to cases and controls with no glaucoma diagnosis before the index date because patients with glaucoma frequently receive cataract extraction as part of their treatment. Third, we stratified our analysis according to the recorded cataract code at the index date: patients with a cataract diagnosis as the first mentioning of their cataract in the records versus patients who had a cataract surgery mentioned first.

Results

We identified 206 931 patients with a first recording of a cataract diagnosis or of cataract surgery. Mean age at the index date was 73.7 years (standard deviation ±10.1 years), and 62% of cases were female. The mean number of years of a history in the database was 12.2 years (standard deviation ±5.6 years). Approximately two thirds (65.9%) of the cases had a cataract diagnosis as the first mentioning of a cataract, and 34.1% had a cataract surgery documented without a previously recorded cataract diagnosis. Some diagnoses (55.6%) were followed by a surgery code (64.1% had the surgery within 1 year after the cataract diagnosis), and a few cataract surgeries were followed by a cataract diagnosis (13.5%).

The main characteristics of cases and controls are displayed in Table 1. Smoking and obesity were not associated with an increased risk of cataract, whereas cardiovascular diseases, diabetes, and glaucoma were associated with increased risk of cataract (Table 1).

Long-term use of SSRI (≥20 prescriptions) compared with nonuse was not associated with an increased risk of cataract: adjusted OR of 1.00 (95% CI, 0.97−1.04) (Table 2). The result was virtually identical for current long-term use (i.e., only those patients with a last SSRI prescription within 30 days before the index date) compared with nonuse of SSRI (adjusted OR, 0.99; 95% CI, 0.94−1.03). The results did not differ between men and women (data not shown); there was a slight suggestion of an increased risk of cataract in individuals aged less than 65 years (long-term SSRI users compared with nonusers: adjusted OR, 1.24; 95% CI, 1.15−1.34). We did not find an increased cataract risk in our analysis of mutually exclusive use of separate SSRIs (Table 3).

Long-term use of TCA exposure was associated with a slightly increased OR for cataract (adjusted OR, 1.15; 95% CI, 1.12−1.19), whereas we found a slightly decreased risk among long-term users of other antidepressants (adjusted OR, 0.80; 95% CI, 0.75−0.85).

The results were similar in the sensitivity analysis in which we shifted the index date by 2 years, in the analysis in which we excluded patients with glaucoma, as well as in the analysis stratified by cataract code (diagnosis vs. surgery) (results not shown).

Discussion

The results of this large observational study suggest that SSRI use is not associated with an increased risk of cataract, neither overall nor in relation to exposure timing or duration.

There have been 2 previous studies of the association between SSRI use and cataract development that reported increased risks of cataract[11,12]: OR of 1.15 (95% CI, 1.08−1.23) for current use of SSRIs[11] and OR of 1.36 (95% CI, 1.23−1.51) for use of ≥1 year of SSRIs.[12] The 2 studies also looked at the effect of individual substances on cataract risk and found ORs of up to 1.39 (95% CI, 1.07−1.80) for current use of fluvoxamine[11] and 1.36 (95% CI, 1.33−1.77) for use of ≥1 year of citalopram.[12] However, the results of our study did not yield an increased risk for SSRIs as a group or for any individual substance. The first study was performed in Canada in a cohort of patients who received a coronary revascularization procedure.[12] Mean age of patients was 73 years, as in the present study. However, generalizability of the study sample may be limited because cases were not drawn from the general